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EDITORIAL COMMENT

Getting to the cART of the Matter

Risk Stratification for Cardiovascular Events With HIV Infection*

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With the success of potent combination antiretroviral therapy (cART), HIV infection has been transformed from a disease with high mortality to one with increasing life expectancy and hence susceptibility to the development of chronic diseases.[1] Despite the effectiveness of cART, a chronic inflammatory state persists in people living with HIV (PLWH), resulting in vascular dysfunction, accelerated atherosclerosis, and myocardial dysfunction. Furthermore, toxicity from cART results in myocardial fibrosis, apoptosis, and steatosis.[2,3] Accordingly, cardiovascular disease is a major cause of morbidity and mortality in PLWH, with reports suggesting approximately 6.5% of AIDS-related mortality is cardiovascular-related.[4]

HIV-associated cardiovascular diseases are diverse, including cardiomyopathy, coronary artery disease, myocarditis, pericardial disease, vasculitis, metabolic syndrome, and pulmonary hypertension, among others.[4,5] Of note, sudden cardiac death (SCD) is an important independent complication,[6] which, in the presence of heart failure, accounts for the majority of cardiac deaths in PLWH.[7-9] From a mechanistic perspective, there is a complex interplay of risk factors resulting in ventricular arrhythmias and potential SCD in PLWH, including medications (eg, antibiotics, antifungals, antidepressants, antipsychotics, antiarrhythmics, methadone, protease inhibitors, and antivirals), illicit drug use, QT interval prolongation, HIV viral suppression (or lack thereof), HIV myocarditis, accelerated atherosclerosis due to HIV with resulting myocardial infarction, chronic inflammation, and myocardial fibrosis.[6,8,10] Of note, while myocardial fibrosis is considered an important substrate for ventricular arrhythmias, its causes overlap with but are not completely the same as those potentially linked to SCD (**Figure 1**).

Predicting SCD is challenging in PLWH, with the diagnosis often made postmortem. This reinforces the importance of identifying subclinical markers in PLWH to stratify the risk of developing cardiomyopathy, ventricular arrhythmias, and SCD. Thus, studies have begun to emerge that explore the clinical correlates of SCD in PLWH. Alvi et al[9] retrospectively examined a heart failure cohort comprising 2,578 patients with HIV from a single center focusing on SCD as the primary outcome, with subgroup analyses based on viral load and left ventricular ejection fraction. A 3-fold increase in SCD was demonstrated in PLWH, with cocaine use, lower left ventricular ejection fraction and absence of beta-blocker prescription identified as predictors.[9] PLWH and heart failure patients who did not have a conventional indication for an implantable cardioverter-defibrillator were shown to have a SCD rate of 10% per year.[9] In another recent study, Tseng et al[7] prospectively evaluated deaths due to out-of-hospital cardiac arrest in people with and without HIV. Of 109 deaths from out-of-hospital cardiac arrest among 610 unexpected deaths in HIV-positive persons, 48 were deemed to be due to SCD, and only 22 were found to have an arrhythmic cause. Drug overdose was more common in persons with HIV (34% vs 13%), and there was greater interstitial myocardial fibrosis in the HIV-positive group.[7]

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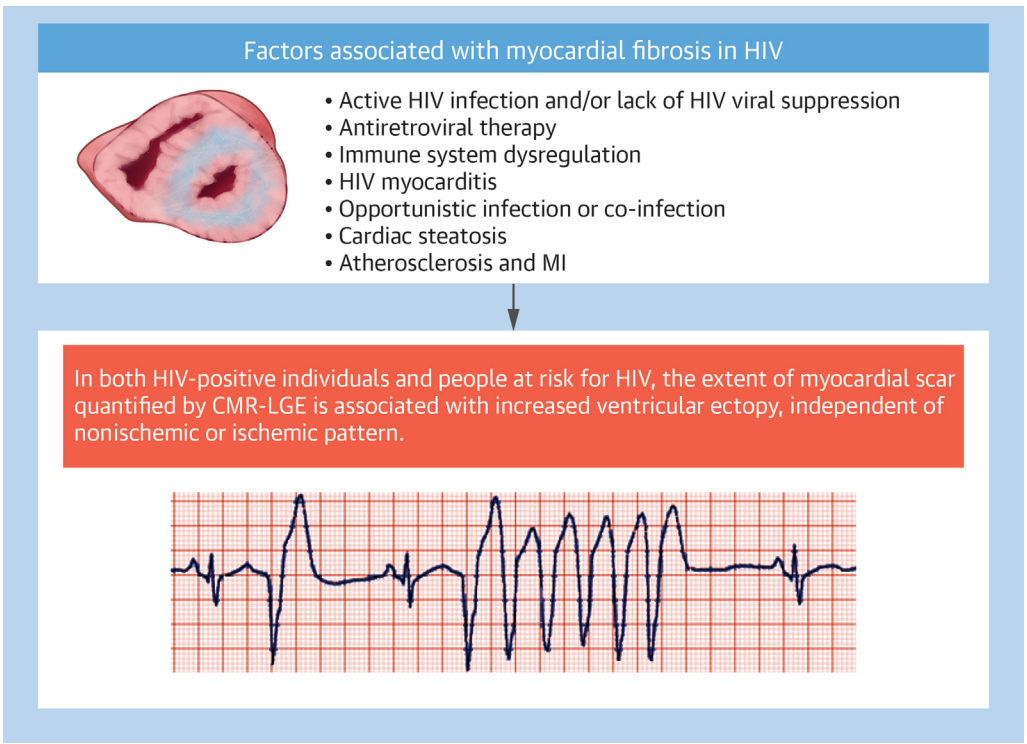
FIGURE 1 Factors Associated With Myocardial Fibrosis in Patients With HIV Infection, and Relationship to Ventricular Ectopy



CMR-LGE = cardiac magnetic resonance-late gadolinium enhancement.

With this as the background, in the current issue of *JACC: Advances*, Mustapha et al[11] present an analysis of the relationship between myocardial scar and ventricular ectopy (VE), a harbinger of SCD, in the context of HIV infection. The burden of VE was evaluated using electrocardiogram patch monitoring (median wear time of 8.3 days) to gain further insight into the impact of subclinical disease-related abnormalities in myocardial substrate on cardiovascular events. The study involved 329 participants (median age 55 years, 30% women, 62% PLWH) recruited from 3 longitudinal U.S. cohort studies, which looked at a combined cohort of PLWH and people without HIV (PWOH) who were at risk for HIV infection (including men who have sex with men and a history of injection drug use). Of the 329 participants, 109 were found to have late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (62% PLWH), with larger scar mass correlating with higher VE burden. These associations were independent of left ventricular structure and function, as well as HIV serostatus, and persisted among PLWH who achieved viral suppression. Specifically, the core outcomes were not related to having or not having HIV.

This builds on the previous work of these authors, which also used cardiac magnetic resonance to characterize myocardial disease in PLWH as compared to PWOH.[12] In that study of 436 participants, despite low LGE-determined scar burden in both PLWH and PWOH, PLWH exhibited an expanded interstitial space as measured by extracellular volume fraction, as well as increased indexed left atrial volumes.[12]

The study of Mustapha et al[11] in this issue of *JACC Advances* contrasts somewhat with a study by Meyer et al,[13] which showed no difference in VE or ventricular tachycardia prevalence between PLWH and PWOH, with the caveat that among PLWH, those with worse viral and immunologic status, based on HIV viral load and lower CD4 count, had an increased likelihood of developing ventricular arrhythmias.[13] This finding was not observed by Mustapha et al[11]; however, their control group comprised PWOH but had risk factors for contracting HIV, reducing sociodemographic bias, a factor that may, in part, account for the observed difference between studies.[11]

Mustapha et al[11] highlight 2 important areas for future research. There is a need for serial measurements of LGE and VE burden, and further longitudinal

follow-up is required to refine risk stratification for heart failure episodes and malignant arrhythmias, as well as other clinical events. Longitudinal clinical trials should, of course, go hand in hand with mechanistic studies to shed further light on the underlying pathobiological processes driving adverse clinical events, which could lead to other means of risk stratification such as biomarkers or other clinical algorithms.

The demonstration that myocardial scar as identified by LGE is associated with VE, independent of HIV status, disease control, and pattern of LGE,[11] is another important step in the risk stratification of cardiovascular events, including SCD, in PLWH. Given the prevalence of SCD in PLWH and the challenges surrounding its assessment, we are presented with compelling evidence for continued research into this challenging condition.

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REFERENCES

1. Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human immunodeficiency virus and heart failure in low- and middle-income countries. *J Am Coll Cardiol HF*. 2015;3(8):579-590.

2. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. *J Infect Dis*. 2012;205(Suppl 3):S375.

3. Nelson MD, Szczepaniak LS, LaBounty TM, et al. Cardiac steatosis and left ventricular dysfunction in HIV-infected patients treated with highly active antiretroviral therapy. *J Am Coll Cardiol Img*. 2014;7(11):1175.

4. Escárcega RO, Franco JJ, Mani BC, Vyas A, Tedaldi EM, Bove AA. Cardiovascular disease in patients with chronic human immunodeficiency virus infection. *Int J Cardiol*. 2014;175(1):1.

5. Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation*. 2002;106(11):1420-1425.

6. Freiberg MS, Duncan MS, Alcorn C, et al. HIV infection and risk of World Health Organization-defined sudden cardiac death. *J Am Heart Assoc*. 2021;10:e021268.

7. Tseng ZH, Moffatt E, Kim A, et al. Sudden cardiac death and myocardial fibrosis, determined by autopsy, in persons with HIV. *N Engl J Med*. 2021;384(24):2306.

8. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. *J Am Coll Cardiol*. 2012;59(21):1891.

9. Alvi RM, Neilan AM, Tariq N, et al. The risk of sudden cardiac death among patients living with heart failure and human immunodeficiency virus. *J Am Coll Cardiol HF*. 2019;7:759-767.

10. Narla VA. Sudden cardiac death in HIV-infected patients: a contemporary review. *Clin Cardiol*. 2021;44(3):316-321.

11. Mustapha A, Peterson TE, Haberlen S, et al. Association between left ventricular scar and ventricular ectopy in people living with and without HIV. *JACC: Adv*. 2023;2(10):100722.

12. Wu KC, Haberlen SA, Plankey MW, et al. Human immunodeficiency viral infection and differences in interstitial ventricular fibrosis and left atrial size. *Eur Heart J Cardiovasc Imaging*. 2021;22:888-895.

13. Meyer A, Dandamudi S, Achenbach C, Lloyd-Jones D, Feinstein M. Ventricular ectopy and arrhythmia characteristics for persons living with HIV and uninfected controls. *J Int Assoc Provid AIDS Care*. 2019;18:2325958219852123.

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